REMARKS

Claims 8, 9, 30, and 32-38 are pending in this application. Claims 8, 9, 30, and 32-38 are rejected. By the present amendment, claim 30 is hereby amended to clarify that the BSMR effector interacts with BSMR. Claim 32 is amended to change its dependency from claim 31 to claim 30, and claims 35 and 36 are amended to delete the term "second." As the amendments are fully supported by the specification as filed, the amendment adds no new matter.

In view of the amendments and following remarks, reconsideration of claims 8, 9, 30, and 32-38 respectfully requested.

Claim Objection

Claims 32 and 38 are objected to as being dependent on a cancelled claim. Applicants submit that the amendment to claim 32 to change its dependency from cancelled claim 31 to claim 30 overcomes the objection.

Claim Rejections-§112

Claim 35 is rejected as lacking antecedent basis. Claim 35 has been amended to delete the term "second". Applicants submit that the amendment overcomes the rejection.

§ 103 Rejections

Claims 8, 9, 30, 32, 37, and 38 are rejected under 35 USC 103 (a) as being unpatentable over Carulli et al. (US Patent NO. 6,780,609)(hereinafter "Carulli et al".) and Dong et al. (1998, Ref B06 in PTO 1449 of 10/15/02) (hereinafter "Dong et al.") in view of Tamai et al. (2000, REF A24 in PTO 1449 of 5/1/02.) (hereinafter "Tamai et al.") Claims 33 and 34 are rejected under 35 USC 103 (a) as being unpatentable over Caurlli et al and Dong et al, in view of Tamai et al and Opperman et al. Claims 35 and 36 are rejected under 35 USC 103 (a) as being unpatentable over Caurlli et al and Dong et al, in view of Tamai et al, further in view of Wang et al, and Hughes et al.

Claim 8 recites a method of regulating bone strength and mineralization by using a ligand that acts on a bone density regulating transmembrane receptor." Amended claim 30 recites a BSMR effector that interacts with BSMR. Thus, the independent claims at issue are concerned

with BSMR as a transmembrane receptor and BSMR ligands or molecules that interact with BSMR. Neither Carulli et al., Dong et al., or Tamai et al., alone or in combination, teach or suggest that LRP5 (i.e., the BSMR of the instant application) is a receptor for Wnt. Nor do these references disclose the other BSMR ligands set forth in claims 8 and 30.

Applicants agree with the Examiner that neither Carulli et al. nor Dong et al. teach the modulation of the BSMR protein by Wnt signaling. Applicants, however, do not agree, that Tamai et al. "disclose that LRP5 is induced by Wnt signaling" (See 1st full paragraph on page 4 of the Final Office Action) or that "Tamai et al. describe the signal transduction of LRP5/LRP6 by Wnt." (Id.)

Tamai et al. draws NO conclusions regarding LRP5. Tamai et al. conducted only one experiment in Xenopus embryos with LRP5. The only comment in Tamai et al. concerning this experiment was as follows: "Although LRP5 alone did not induce axes, co-injecting LRP5 and Wnt-5a did. (See second paragraph on page 531 of Tamai et al. Tamai et al. did not conclude that LRP5 mediates, or is directly or physically involved, in Wnt signaling because the effects observed by merely co-injecting LRP5 and Wnt-5a are insufficient, in themselves, to establish any role for LRP5 in mediating Wnt signaling. After conducting a series of experiments involving only LRP6, Tamai's only conclusion regarding proteins in the LRP family was that "**LRP6** may be a component of the Wnt receptor complex." (abstract, emphasis added.) Tamai **did not** make a similar conclusion regarding LRP5 because a single co-injection experiment does not tell an artisan whether the LRP5 protein is involved in the Tamai model of Wnt/β-catenin signaling.

There are many different members in the Wnt family and there are two Wnt signaling pathways. One pathway, known as the canonical pathway, involves the binding of Wnt to a cell receptor, transduction of this signal by the receptor and a resultant inhibition of the degradation of β-catenin inside the cell. A second Wnt signaling pathway, known as the non-canonical pathway, does not involve a Wnt receptor or β-catenin. Claim 8 recites a method of regulating bone strength and mineralization by using a ligand that acts on a bone density regulating transmembrane receptor." Amended claim 30 recites an effector that interacts with BSMR. Thus both claims are only concerned with the canonical pathway because they require an interaction between BSMR, as a receptor, and its ligand (e.g. Wnt). This is supported by the specification. For example, the specification states "[a] fourth discovery is that certain

extracellular ligands can modulate the activity of this [BSMR] protein and can be applied as therapeutic agents for improving bone strength and mineralization." (¶ 0028.) The specification goes on to explain that "Figs 10 -12 show data obtained from the use of effectors from the Wnt/beta-catenin signaling pathway acting upon" the cells used in the study (¶ 0080); explaining that "in particular embodiments of the invention an effector of the BSMR . . . is administered together with one of these other gene products. In particular, genes and their encoded products that are targets of Wnt/beta-catenin signaling . . ." (¶ 0083); or explains that "it is believed that BSMR functions as a Wnt co-receptor in the canonical signaling pathway that employs beta-catenin as a downstream effector" (¶ 0088) (all emphases added). In contrast, Tamai et al. do not teach or suggest that LRP5 is a Wnt ligand or a Wnt co-receptor, or even that Wnt is an effector of LRP5. Therefore, the Tamai et al. disclosure, alone or in combination with Caurlli et al. and Dong et al., does not make claims 8 and 30 obvious.

In contrast to LRP6, which Tamai et al. studied extensively, Tamai et al conducted only one experiment with LRP5. To illustrate, here is a list of experiments Tamai et al used to establish the role of LRP6 in Wnt signaling in Xenopus embryos, none of which involved LRP5. In one experiment, Tamai et al. examined the effect of LRP6 on neural crest formation in Xenopus. Tamai et al. then conducted experiments to see whether LRP6 functions in Wnt-responding or Wnt-producing cells of Xenopus embryos, and concluded tha " LRP6 is probably involved in responding, rather than in enhancing, the production or secretion of the Wnt ligand" (See sentence bridging page 531 and 532 in Tamai et al., Emphasis added) In another series of experiments, Tamai generated a mutant of LRP6 and then speculated "that the LRP6 cytoplasmic domain is required for Wnt signaling", and that "probably other (Fz) molecules that mediate Wnt-1 or Wnt-8 signaling depend on LRP6", that the mutant LRP6 molecule "interferes specifically with Wnt signaling", and that therefore, "LRP6 is required for Wnt-dependent neural crest formation" in Xenopus embryos. (See first full paragraph on page 532 of Tamai et al., Emphasis added.) Finally, to show if LRP6 may be acting as a co-receptor for Wnt-molecules, Tamai conducted another series of experiments which involved measuring the binding of LRP6 (and not LRP5) to Wnt-1 and Fz. (See page 533 of Tamai et al.) Only after conducting all these experiments did the authors interpret their results and conclude that LRP6 is a component of the Wnt receptor complex. **None** of the experiments enumerated above were performed with LRP5. Not only did Tamai et al. not perform the same experiments on LRP5 or make any conclusions

regarding the role of LRP5 in Wnt signaling, the authors did not even suggest such a role for LRP5.

Even if one could argue that Tamai et al. would motivate a skilled artisan to explore the relationship between Wnt and LRP5, neither Tamai, nor Carulli or Dong, provide a reasonable expectation of success regarding the role of Wnt as an LRP5 ligand in bone formation. As previously stated, LRP5 and LRP6 share only 71% homology. As one of ordinary skill in the cell biology art would understand and appreciate, 71% homology between two proteins is insufficient to reasonably predict that the two proteins would have the same binding partners. Moreover, and perhaps more importantly, a 71% sequence homology between two proteins is insufficient for one of ordinary skill in the art to reasonably predict whether binding of a particular ligand to both proteins would have the same effect, i.e., that such a ligand would activate both proteins. Thus, one of ordinary skill in the art, upon reading Tamai et al. would understand and appreciate that the statements made in Tamai et al. about the relationship between Wnt and LRP6 cannot be used to reasonably predict that Wnt and LRP5 would have the same relationship. Indeed, Tamai et al. end their article by stating that "whether other LRPs and LRP-binding proteins participate in or modulate different Wnt-Fz signaling pathways needs evaluation. The LRP family have diverse signaling functions." (page 534, emphasis added.) Moreover, the Tamai et al. experiments showed that LRP5 functions differently from LRP6 in Xenopus embryos because administration of 2 ng of LRP6 alone induced *Xenopus* axis duplication whereas administration of 2 ng of LRP5 alone did not (Fig. 1a, p. 531), highlighting the difference between the LRP6 and LRP5 proteins and their effects.

In addition, Tamai et al. is directed to the effect of Wnt/LRP6 in embryonic development in *Xenopus*. Tamai et al. do not provide any guidance about the role, if any, that LRP6, plays postnatally in differentiated osteoblasts of adult animals. Tamai et al. does not teach or suggest that LRP6, much less LRP5, is a signal transducer for Wnt in osteoblasts or bone forming cells in any cell, much less bone forming cells of an animal after birth. Tamai et al.'s experimental results obtained in *Xenopus* embryos during embryogenesis cannot be extrapolated to the complex mechanisms involved in adult human bone homeostatic events, even if the effector molecules and receptors were the same, which in this instant, they are not. Accordingly, there is nothing in Tamai et al. to suggest that LRP6, much less LRP5, would act as a signal transducer for Wnt in bone forming cells of patients with osteoporosis.

In sum, neither Carulli et al., nor Dong et al. or Tamai et al., alone nor in combination, teach or suggest that BSMR is a receptor for Wnt. Carulli et al. does not identify any molecules that bind to BSMR in bone forming cells. Similarly, neither Carulli et al., Dong et al., nor Tamai et al., identify any molecules that act as BSMR ligands capable of regulating bone strength and mineralization (as recited in claim 8), or that increase alkaline phosphatase activity in bone forming cells (as recited in claim 30). Thus, even if one combined Carulli et al., Dong et al. and Tamai et al., one would not arrive at all the steps in claim 8 or 30. Moreover, one of ordinary skill in the art who is aware of the teachings in these three references would not reasonably expect that BSMR would mediate Wnt signaling in bone forming cells, let alone that administration of a WNT protein to a patient with osteoporosis would have a beneficial effect on bone development and mineralization in such individuals. Accordingly, Caurlli et al., Dong et al. or Tamai et al., alone or in combination, do not render the methods recited in claims 8 and 30 obvious.

Claims 9, 32, 37 and 38 depend from claims 8 or 30 and so, for at least the same reasons stated above, these claims are also non-obvious. Neither Opperman et al, nor Wang et al. nor Hughes et al. provide the teachings or suggestions that are absent from Carulli et al, Dong et al, and Tamai et al. Accordingly, claims 33, 34, 35, 36, also are not obvious in view of the references applied by the Patent Office.

Applicants submit that claims 8, 9, 30, and 32-38 are now in condition for allowance. Prompt notice of such allowance is respectfully requested. If the Examiner has any questions regarding the amendments, he is encouraged to call Pamela A. Docherty at (216) 622-8416.

Respectfully submitted,

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By: Kristin J. Frost
Kristin J. Frost, Reg. No. 50,627
(216) 622-8895